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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/677,495

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Chun L. Gao

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10/15/2007

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EXAMINER

SANG, HONG

ART UNIT

PAPER NUMBER

1643

MAIL DATE

DELIVERY MODE

10/15/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/677,495

Applicant(s)

GAO ET AL.

Examiner

Hong Sang

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 August 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18, 20 and 38-53 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-18, 20, and 38-53 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- 1) ☐ Certified copies of the priority documents have been received.
 - 2) ☐ Certified copies of the priority documents have been received in Application No. _____.
 - 3) ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) ☒ Notice of References Cited (PTO-892) | 4) ☐ Interview Summary (PTO-413) |
| 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) ☐ Information Disclosure Statement(s) (PTO/SB/08) | 5) ☐ Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) ☐ Other: _____ |

DETAILED ACTION

RE: Gao et al.

1. Applicant's response filed on 8/22/07 is acknowledged. Claims 1-18, 20 and 38-53 are pending. Claims 19, and 21-37 are cancelled.
2. Claims 1-18, 20 and 38-53 are under examination.

Objections Withdrawn

3. The objection to the specification because applicants fail to update the status (pending, allowed, etc.) of all parent priority applications in the first line of the specification is withdrawn in view of applicant's amendment to the specification.

Rejections Withdrawn

4. The rejection of claims 17 and 51 under 35 U.S.C. §103(a) as being unpatentable over Gao et al. (Urology, 1999, 53: 714-721), in view of Terstappen et al. (US Patent 6,365,362, effective filing date at least 2/12/1999), Croce et al. (US Patent 5,674,682, Date of Patent: 10/7/1997), Katz et al. (US Patent 5,840,494, Date of Patent 11/24/1998), and Tso et al. (WO 97/38313, international publication date: 10/16/1997) is withdrawn in view of the new grounds of rejections.

Response to Arguments

5. The rejection of claims 1-16, 18, 20, 38-50 and 52-53 under 35 U.S.C. §103(a) as being unpatentable over Gao et al. (Urology, 1999, 53: 714-721), in view of

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Terstappen et al. (US Patent 6,365,362, effective filing date at least 2/12/1999), Croce et al. (US Patent 5,674,682, Date of Patent: 10/7/1997), Katz et al. (US Patent 5,840,494, Date of Patent 11/24/1998), and Tso et al. (WO 97/38313, international publication date: 10/16/1997) is maintained.

The response states that the Examiner has relied on impermissible hindsight in an attempt to demonstrate an "apparent reason to combine known elements in the fashion claimed." The response states that the cited references fail to provide motivation to combine so many separate pieces of so many separate references, but these references, taken independently or in combination, do not contain the sensitivity element of every independent claim (1, 20 and 42) or "SEQ ID NO 3 and SEQ ID NO 4" as recited in claims 17 and 51. The response states that the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In fact, the level of sensitivity achieved by the claimed invention has never heretofore been disclosed or suggested, and the problem of high false positive rates using PSA tests under conditions known in the art has not been solved or at least substantially improved by those skilled in the art.

Applicants' arguments have been carefully considered but are not persuasive. "Any judgment on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." *Ln re McLaughlin* 443. F.2d 1392, 1395, 170 USPQ 209, 212

(CCPA 1971). In the instant case, Gao et al. disclose a method to detect PSA-expressing prostate cancer cells as low as one cell in 10 million lymphocytes (1×10^7), see Abstract, lines 6-8; page 715, right column, Determination of PCR Sensitivity section, lines 6 and 7). Gao et al. teach that using their PCR conditions, they could confidently detect LNCaP cells to lymphocytes in a ratio of 1 LNCaP cell per 10^7 lymphocytes (see page 715, right column, Determination of PCR Sensitivity section, lines 6 and 7). In Gao's study, none out of the 22 controls was RT-PCT-PSA positive, thus the false positive rate of Gao's study is zero (see previous office action page 5, 2nd paragraph). Terstappen et al. teach a method for detection and enrichment of prostate cancer specific cells from blood sample, said method comprises use of immunomagnetic beads (dynal magnetic beads) to isolate said cells (see column 8, lines 11-53). Terstappen et al. teach that their assay can detect one epithelial cell or less in 1 ml of blood (see abstract). It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Gao et al. to first enrich the prostate tumor specific cells that are present in blood and then perform RT-PCR in view of the teachings of Terstappen et al. A person of ordinary skill in the art would have been motivated to modify the method of Gao et al. by incorporating the step of enriching tumor specific cells as taught by Terstappen et al. for the purpose of increasing the sensitivity of the method and reducing the background. This is a well-known strategy for detecting rare cells in blood, as evidenced by the teachings of Tso et al. Tso et al. teach a method for enriching rare cells in a fluid comprising the rare cells (that are preferably rare non-blood cells) and non-rare cells,

and further identifying the rare cells (see page 3, lines 3-5 and 21-23). One of ordinary skill in the art would have a reasonable expectation of success to do so because Terstappen et al. teach how to enrich prostate cancer cells in a sample of blood and Gao et al. teach how to detect PSA mRNA using RT-PCR. Thus the use of the method of Terstappen to enrich the blood prostate tumor cells before RT-PCR detection, was clearly in the purview of those of ordinary skill in the art and was within the knowledge of 'those in the art at the time the invention was made.

While the prior art does not disclose that the sensitivity is at least 80% or greater, the sensitivity limitation is recited in a wherein clause, which in the instant case could be interpreted as inherent results of the active steps. The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. In *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a "whereby" clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." *Id.* However, the court noted (quoting *Minton v. Nat 'l Ass 'n of Securities Dealers, Inc.*, 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed.Cir. 2003)) that a "whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited." *Id.* (see MPEP 2111.04[R-3]). In the instant case, the claims recite that the method is capable of detecting one PSA-expressing cell in one ml of blood or 10^7 lymphocytes. Gao et al. teach that using their PCR conditions, they could confidently detect LNCaP cells to lymphocytes in a ratio of 1 LNCaP cell per 10^7 lymphocytes (see page 715, right column, Determination of PCR Sensitivity section,

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lines 6 and 7). The false positive rate in Gao et al. is zero, indicating true positives/true positives plus false positives is 100% (see previous office action, page 5). Furthermore, Terstappen et al. disclose that their method for detection and enrichment of prostate cancer specific cells from blood sample can detect one epithelial cell or less in 1 ml of blood (see abstract). Thus, one skilled in the art would expect the combination of Gao and Terstappen et al. would provide much more sensitive method than any of Gao and Terstappen alone. Because the method steps taught by the prior art appear to be the same as the instantly-claimed, and because the instant claims do not set forth any active steps which differentiate the instant invention from the method of the prior art, by performing the method steps of the prior art, one would expect to achieve the same sensitivity. Because of these reasons, the rejection is deemed proper and therefore, maintained.

New Grounds of Rejections

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 1-18, 20 and 38-53 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gao et al. (Urology, 1999, 53: 714-721), in view of Terstappen et al.

(US Patent 6,365,362, effective filing date at least 2/12/1999), Croce et al. (US Patent 5,674,682, Date of Patent: 10/7/1997), Katz et al. (US Patent 5,840,494, Date of Patent 11/24/1998), and Tso et al. (WO 97/38313, international publication date: 10/16/1997), further in view of Buck et al. (Biotechniques, 1999, 27(3): 528-536).

The teachings of Gao, Terstappen, Croce, Katz, and Tso et al. have been set forth above as they apply to 1-16, 18, 20, 38-50 and 52-53 (see previous office action mailed on 2/22/07 and paragraph 5 above). Croce et al. disclose a method for detecting prostate cancer in a patient, wherein the method comprises isolating epithelial cells from a sample of blood from said patient, lysing epithelial cells and isolating nucleic acid, conducting RT-PCR on said isolated nucleic acid using a set of primers including SEQ ID NO.9, Taq polymerase to synthesize cDNA, conducting PCR on said cDNA using PSA-specific primers and Taq polymerase and detecting amplified PSA gene (see column 3, lines 35-66; column 9, lines 15-67; column 10, lines 1-20), wherein the primer SEQ ID NO: 9 contains specific exons of the PSA gene which include instant claimed SEQ ID NO: 4 (see column 3, lines 56-66; column 12, lines 45-55, see previous office action for the sequence alignment Exhibit A). Tso et al. teach a PSA-specific probe (SEQ ID NO: 3) that comprises the instant SEQ ID NO: 3 (see sequence alignment Exhibit B, page 21, lines 2-5, 219-28; page 48, claims 11 and 13). Tso et al. teach that the probes can be used for PCR to identify or detect rare cancer cells (see page 20, lines 15-21). Because the instant claims 17 and 51 use the term "comprises" which is open, the primers of Croce and Tso et al. read on the instant invention.

The prior art does not disclose to use the primer set consisting of SEQ ID NOs.3 and 4, however, it is considered to be obvious in view of the teachings of Buck et al.

Buck et al teaches a study wherein 69 different primer sequences submitted by 39 different laboratories and 95 control primers distributed at 3 base pair intervals across a 300 base pair oligonucleotide test sequence were analyzed (pages 528-529, in particular). It was determined that all the submitted primers functioned very well and almost all the "control" primers functioned very well (page 533). Only one "control" primers functioned poorly; however, the poorly performing control primer performed adequately under optimized conditions (page 533). Thus, under optimal sequencing conditions with highly pure template and primer, many of the commonly applied primer design parameters are dispensable (see page 528, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to detect PSA with the primers set forth in SEQ ID NOS 3 and 4 because the Croce et al. teach the primer comprising SEQ ID NO.4, and Tso teach a PSA specific probe SEQ ID NO.3, which comprises instant SEQ ID NO.3, and Buck et al teach that, due to the new generation of sequencing reagents (page 528, in particular), sequences throughout a known oligonucleotide would be obvious choices to design a primer.

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column

2).” Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success. In the instant case, Croce et al. teach the primer comprising SEQ ID NO.4 and Tso et al. teach a PSA specific probe comprising SEQ ID NO.3. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Conclusion

8. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

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For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Hong Sang, Ph.D.
Art Unit 1643
Oct. 8, 2007

/Christopher Yaen/
Primary Examiner
Art Unit 1643
October 10, 2007